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Guest Editorial

Examining the role of microvesicles to develop prognostic and diagnostic assays

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Early disease detection is a logical, imperative goal necessary to improve dramatically the patient's odds for successful treatment strategies, survival and overall increase the quality of life. Given the continuous increase in health care cost mostly due to therapy focused on end stage sequelae of diseases rather than prevention and early detection, it has become increasingly clear that existing methods are limited and falling short of these goals. Therefore, there is urgent need to develop new prognostic and diagnostic assays that can detect initial stages of disease, predict accurately high and low risk patients as well as early patient response to therapy. The increased knowledge of microvesicle biology and the ability of microvesicles to enrich tissue-specific biomarkers, both in normal and pathological conditions suggest that they may provide a valuable avenue to identify diagnostic signatures, develop new diagnostic assays and help guide therapeutic approaches.

Microvesicle formation is part of constitutive biological processes, such as turnover of intracellular and surface membranes during endocytosis and exocytosis, and normal cellular response to complement attack. Microvesicles are found in significant amounts in plasma, urine, cerebrospinal fluid and broncho-alveolar lavage fluid. Fragile molecules such as RNA molecules show resistance to degradation by RNAases in body fluids when packaged within microvesicles. For years identified as useless cellular debris, recent data seem to challenge the accepted dogma proposing a novel role for microvesicles, as conveyors of information among cells, tissues and even organs through horizontal transfer of proteins, lipids, and nucleic acids. As microvesicles are gaining increasing attention in the basic science circles as an alternative means of intercellular communication, they might also offer a novel way to think about disease detection and treatment. The variety of nucleic acids, proteins and lipids present in microvesicles has the potential to yield signature molecular patterns informative of the state of the human physiology or disease condition. Indeed, it has been recently shown that certain tumors shed microvesicles, which are rich in signaling molecules, second messengers, and genetic material that together constitute a unique, specific, and readily identifiable signature.

Subsequently, microvesicles have been proposed as a novel biomarker source for various

types of cancers. To date, specific cancer markers have been detected in microvesicles isolated from peripheral blood of colorectal and oral cancer patients. Unfortunately, these markers were not consistently detected in early stage cancers. The insufficient early stage cancer biomarker detection in microvesicles may result from the early tumor's isolation from the circulation, which limits the passive diffusion of microvesicles into the blood. Also complicating detection is the further dilution of the tumor-derived microvesicles by the natural shedding of microvesicles by all the cells that are in direct contact with the blood. Moreover, complement-mediated microvesicle formation, which constitutes a major mechanism for microvesicle release, is significantly inhibited in tumor cells due to up-regulation of complement regulatory proteins upon malignant transformation. Although saliva is currently not a mainstream diagnostic body fluid, recent studies have shown that genetic analysis of various components of saliva, such as microvesicles have the ability to discriminate and efficiently detect certain disease. Ideally, molecular characterization of microvesicles would allow a non-invasive sample source for early disease diagnosis, prognosis, as well as for monitoring treatment strategy and efficacy. Tumor-derived microvesicles remain an enticing source of biomarkers for tumor detection, prognosis and therapy monitoring. However, their role in cancer testing will require new methods of peripheral blood and saliva enrichment.

In summary, microvesicles are multifunctional entities that appear to play an active role in many significant biological processes such as regulation of immune response, antigen presentation, transfer of bioactive molecules between cells and tissues, and transfer of viruses and prions. Further investigations into cellular and molecular mechanisms of microvesicle biogenesis and function are needed to increase their efficacy as therapeutic tools. New and more efficient means of nucleic acid profiling of tumor microvesicles have the potential to be useful as biomarkers for screening and biopsy profiling. Although, microvesicles can be easily identified by their size and physical characteristics from biological fluids for diagnostic purposes, further research and proper validation is needed in order for them to be useful in the clinical setting.